IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Albert Charles GYORKOS et al.
Serial No.: 10/577,334 Group Art Unit:
Filed: April 28, 2006 Examiner:
For: NITROGEN-CONTAINING FUSED
HETEROCYCLIC COMPOUNDS

DECLARATION UNDER 37 CFR Sec. 1.132

Honorable Commissioner of Patents and Trademarks
P.O. Box 1450, Alexandria, VA 22313-1450

Sir,

I, Kazuyoshi ASO, a citizen of Japan residing at 10-5-307, Kamihamuro 1-chome, Takatsuki-shi, Osaka, Japan, declare and say that:

1. I was born on September 11, 1963 in Fukuoka, Japan;
2. I graduated from Kyushu University, with degree of Master of Pharmaceutical Science in March 1989;
3. I have been employed by Takeda Chemical Industries, Ltd., Osaka, Japan, since April, 1989, and have been engaged in research and development in the Pharmaceutical Research Division of said company;
4. I was visiting scientist in SmithKline Beecham Pharmaceuticals (Philadelphia, PA) from July, 1996 to October, 1996;
5. I was visiting scientist in Array Biopharma Inc. (Boulder, CO) from June, 2003 to April, 2004;
6. I have been appointed Research Head of Medicinal Chemistry Research Laboratories in said Pharmaceutical Research Division since 2004;

7. I am a member of the Pharmaceutical Society of Japan, and published with other research workers, a number of reports on scientific studies, among others, including

1) Competitive Intramolecular [4+2] Cycloaddition and Tandem [2+2]Cycloaddition / [3,3]-Sigmatropic Rearrangement Sequence of Allenyl 3-Vinyl-2-cyclohexenyl Ethers: Evidence for Switching of the Reaction Pathway by the Substituent Effects; *J. Am. Chem. Soc.* 111, 5312-5320 (1989)

2) Synthesis and Antitumor Activity of Pyrrolo[2,3-d]pyrimidine antifolates with a Bridge Chain Containing a Nitrogen Atom; *Chem. Pharm. Bull.* 43, 256-261 (1995)

3) Novel Pyrrolo[2,3-d]pyrimidine Antifolate TNP-351: Rapid Uptake and Polyglutamate Formation, and High Affinity for Reduced-folate Transport System in Murine Tumor Cells; *J. Takeda. Res. Lab.* 54, 97-107 (1995)

4) Recombinant *Plasmodium falciparum* dihydrofolate reduced-based *in vitro*screen for antifolate antimalarials; *Mol. Biochem. Parasitol.* 81, 225-237 (1996)

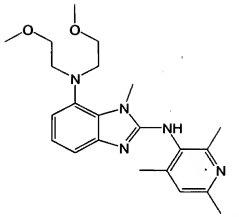
5) Enzyme-inhibition system for identifying potential antimalarials that target highly drug-resistant mutants of *Plasmodium falciparum* dihydrofolate reductase; *Parasitology International* 47, 65-78 (1998)

6) Pyrrolo[2,3-d]pyrimidine thymidylate Synthase Inhibitors: Design and Synthesis of One-Carbon Bridge Derivatives; *Chem. Pharm. Bull.* 49, 1280-1287 (2001);

8. I am one of the co-inventors of the above-identified application Serial No. 10/577,334 and familiar with the subject matter thereof.

9. In order to reconfirm the chemical structure of the compound obtained in Example 117 of the present application, the following Experiment was conducted by myself and under my supervision and control. The compound of Example 117 for test was prepared according to the description of the specification.

(1) The chemical structure of the compound of Example 117 described in the specification as filed was determined as follows based on the ^{1}H-NMR spectral data shown in Fig. 1 attached hereto (Sample name: E10518-10-HCl).



[Structure determined first]

(2) Later on, to reconfirm the above structure, ^{13}C-NMR spectrum, Nuclear Overhauser Effect (NOE) spectra and the like were additionally measured using the same sample as in above (1) (Sample name: B10518-10-HCl).

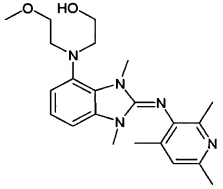
Obtained NMR spectra are shown in Figs. 2 to 12, and the chemical shift data and correlation among atoms derived therefrom are summarized in Table 1. Figs. 1 to 12 and Table 1 are attached hereto, and

Fig. 1 shows ^{1}H-NMR spectrum measured in $CDCl_3$ (400MHz).
Fig. 2 shows ^{13}C-NMR spectrum measured in $CDCl_3$.
Fig. 3 shows ^{1}H-NMR spectrum measured in DMSO-d_6 (300MHz).
Fig. 4 is an expanded chart of the ^{1}H-NMR spectrum of Fig.3.
Fig. 5 to 10 show ^{1}H-^{13}C HMBC (Heteronuclear Multiple-Bond Correlation) spectra measured in DMSO-d_6.
Fig. 11 and 12 show NOESY (NOE correlated Spectroscopy) spectra measured in DMSO-d_6.

The chemical shift values for each atom of the compound were determined from the spectral charts of Figs. 2 to Fig. 4, and summarized in Table 1. The handwritten numeral in the charts indicates the number of the atom shown in the structural formula of Table 1. Namely, the number on the peak shown in the chart suggests that the peak is derived from the numbered atom of the compound.

The correlations among atoms of the compound such as NOE and long range coupling were assigned based on the spectral charts of Figs. 5 to 12, and indicated by arrows in the structural formula of Table 1. The numbers in the chart indicate each numbered atom in the structural formula of the compound.

As seen in the correlationship shown in Table 1, the spectral data of Fig. 5 to 12 show that there are two kinds of methyl group attached to nitrogen atom. Thus, the chemical structure of the compound of Example 117 should be assigned as follows:



[Structure determined finally]

10. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 20 th day of July, 2007

Kazuyoshi ASO